Synthesis of Prostaglandin A_2 through Reaction of 3-*endo*-Bromotricyclo[3.2.0.0^{2,7}]heptan-6-one with a Cuprate Reagent

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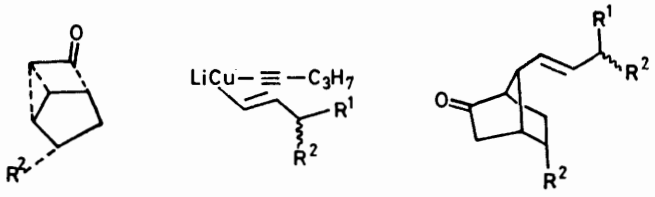
The bromo-ketone (4) reacted with the cuprate reagent (2) to give the norbornanone (5). Two ways of converting the ketone (5) into the unsaturated lactone (8) were discovered. The lactone (8) was converted into the hydroxy-aldehyde (9) *en route* to 9-deoxa-9,10-didehydroprostaglandin D_2 (10) and into prostaglandin A_2 (12) *via* the γ-lactone (11).

TRICYCLO[3.2.0.0^{2,7}]HEPTAN-6-ONES react readily and specifically with nucleophiles.[1] We have shown previously that *endo*-3-t-butyl-dimethylsilyloxytricyclo-[3.2.0.0^{2,7}]heptan-6-one (1) reacted with the cuprate reagent (2) to give the norbornanone (3) and that this



(1) (2) (3)

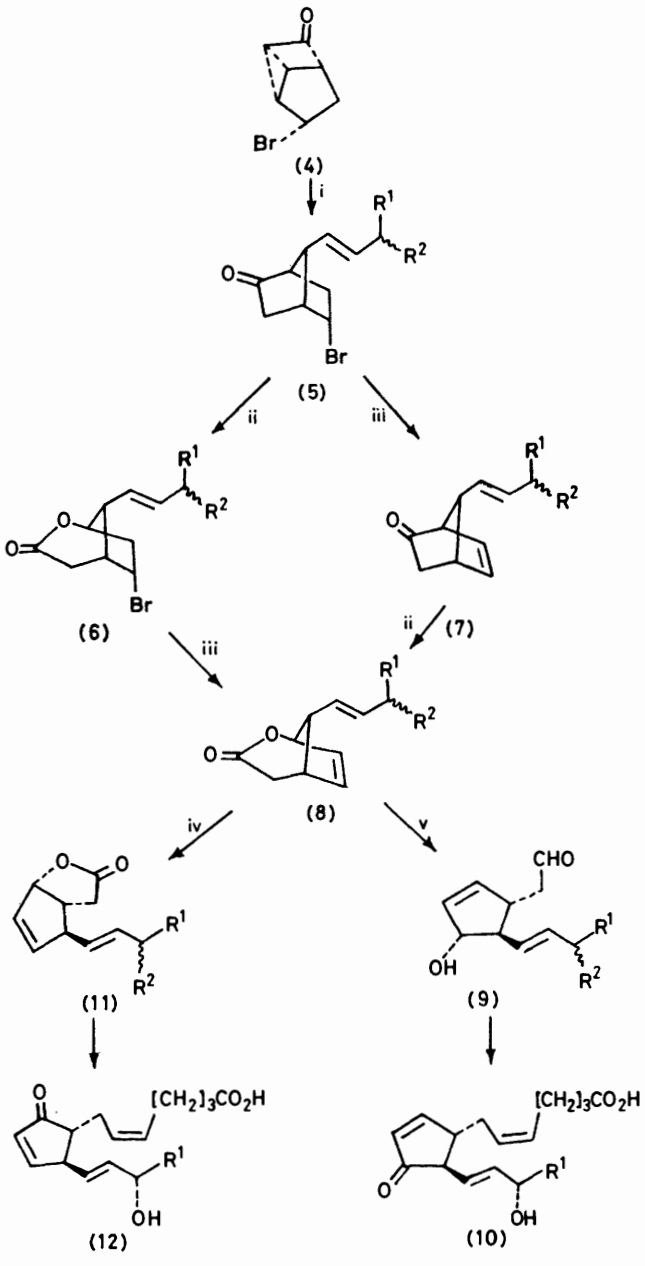
$R^1 = C_5H_{11}$ $R^2 = OSiMe_2Bu^t$

ketone could be converted into prostaglandin C_2, D_2, E_2, and $F_{2\alpha}$.[2,3] In this paper we describe the conversion of *endo*-3-bromotricycloheptan-6-one (4)[4] into prostaglandin A_2 (12) and 9-deoxa-9,10-didehydroprostaglandin-D_2 (10) (Scheme 1).[5]

RESULTS AND DISCUSSION

The ketone (4) was dissolved in ether and methylene chloride at −78 °C and treated with the heterocuprate reagent (2) for 3 h. After work-up and chromatography the norbornanone (5) was isolated in 68% yield. Oxidation of the ketone (5) with *m*-chloroperoxybenzoic acid gave a quantitative yield of an oil which was homogeneous by t.l.c. but was shown to contain two components (ratio 3 : 1) by g.l.c. N.m.r. spectroscopy indicated that the major component was the lactone (6) and suggested that the minor component was the isomer (13). Treatment of the mixture of lactones with diazacycloundecene (DBU) in hot toluene gave, after chromatography, only the lactone (8) (60%). No product(s) derived from the lactone (13) could be found: we suggest that the lactone (13) was preferentially hydrolysed by trace amounts of water in the reaction mixture to give water-soluble material. The preferential hydrolysis of 3-oxabicyclo[3.2.1]octan-2-ones in the presence of 2-oxabicyclo[3.2.1]octan-3-ones has been observed previously.[3]

Conversion of the bromo-ketone (5) into the unsaturated lactone (8) could be accomplished by initially dehydrobrominating the ketone (5) by refluxing in



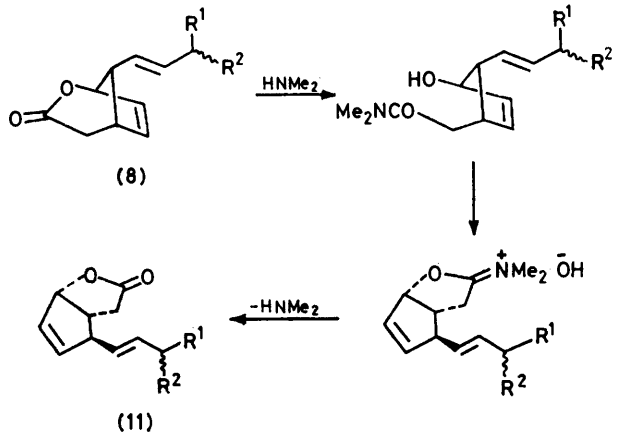
$R^1 = C_5H_{11}$, $R^2 = OSiMe_2Bu^t$

SCHEME 1 *Reagents:* i, (2); ii, *m*-$ClC_6H_4CO_3H$; iii, diazabicycloundecene; iv, heat, Me_2NCHO; v, $AlHBu^i_2$

xylene containing DBU for 4 days. This gave the norbornanone (7) which underwent regiospecific Baeyer–Villiger oxidation to give the lactone (8).

The δ-lactone (8) was reduced to the hydroxy-aldehyde (9) using di-isobutylaluminium hydride (Dibal): a small amount of the diol (14) was formed also but this impurity could be removed by chromatography. The hydroxy-aldehyde (9) was identical (i.r., n.m.r., and t.l.c.) to authentic material [6] and could be converted into 9-deoxa-9,10-didehydroprostaglandin-D_2 (10).

The lactone (8) did not react cleanly with acid [7] but gave the γ-lactone (11) (62%) on refluxing in dimethylformamide (DMF) followed by resilylation. The rearrangement (8) to (11) did not occur in other high-boiling solvents suggesting that the small amount of dimethylamine present in DMF may be responsible (Scheme 2). The γ-lactone (11) was identical (i.r., n.m.r., and t.l.c.) with authentic material [8] and was converted into prostaglandin A_2 (12).

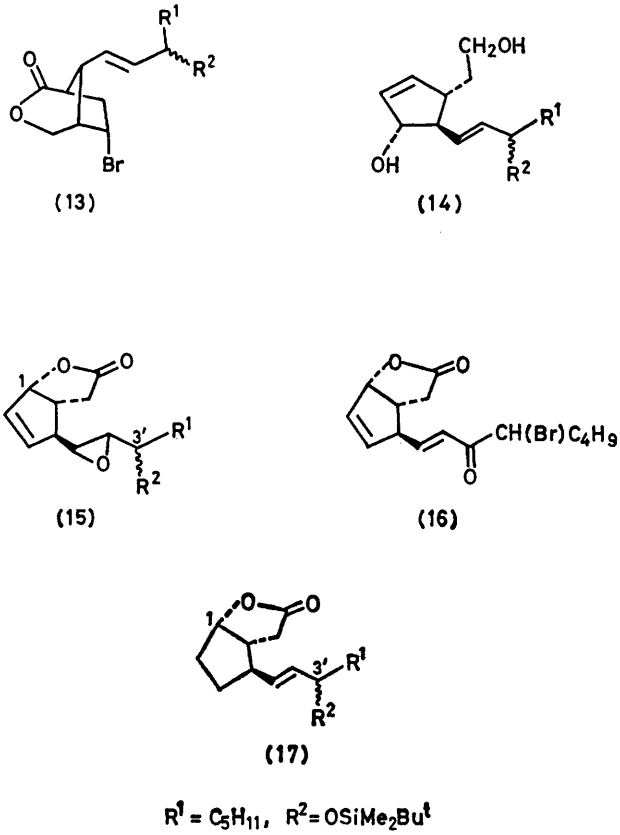


SCHEME 2

The action of other reagents on the γ-lactone (11) was investigated. For example, *m*-chloroperoxybenzoic acid in methylene chloride buffered with sodium hydrogencarbonate converted the lactone (11) [δ($CDCl_3$) *inter alia* 5.50 (3 H, m, H-1′, H-2′ and H-1), 4.08 (1 H, m, H-3′)] into the epoxy-lactone (15) (85%). The site of epoxidation was indicated by n.m.r. spectroscopy [δ($CDCl_3$) *inter alia* 5.45 (1 H, m, H-1) and 3.6—2.2 (7 H, m, H-3′ and six other protons)].

Irradiation of the lactone (11) in carbon tetrachloride containing *N*-bromosuccinimide gave a mixture of products from which the bromo-ketone (16) was isolated in 27% yield by chromatography. We believe that the bromo-ketone (16) is formed by initial desilylation involving HBr present in the solution. Oxidation by *N*-bromosuccinimide of the allylic alcohol so formed and acid-catalysed α′-bromination of the resultant α,β-unsaturated ketone would then lead to the observed product.

The lactone (11) was hydrogenated in tetrahydrofuran at room temperature using 5% rhodium on alumina [9] as the catalyst. When one equivalent of hydrogen had been taken up, the catalyst was removed and the solvent evaporated. The n.m.r. spectrum of the residual oil indicated that the endocyclic double bond had been reduced to afford the lactone (17) [δ($CDCl_3$) *inter alia* 5.10 (1 H, m, H-1) and 4.15 (1 H, m, H-3′)]. A small quantity of a second product was obtained also: while this compound was not fully characterised n.m.r. spectroscopy suggested that it was the fully saturated lactone.



EXPERIMENTAL

^{1}H N.m.r. data refer to solutions in deuteriochloroform and were determined using a Varian EM360 or Perkin-Elmer R-32 instrument. I.r. spectra were recorded using a Perkin-Elmer 297 spectrophotometer for neat films. Distillations were accomplished using the Kugelrohr system. T.l.c. was carried out with Camlab Polygram pre-coated silica-gel plates. Thick-layer chromatography was performed on Anachem Uniplates. Short-column chromatography used Merck Kieselgel H. G.l.c. analysis was performed on a Hewlett-Packard 5880A instrument using a 4-m OV-225 column at 240 °C. Mass spectra were determined after ionisation by electron impact at 70 eV (e.i.m.s.) or chemical ionisation using ammonia (c.i.m.s.). Light petroleum refers to the fraction of b.p. 60—80 °C, and all solvents for chromatography were distilled before use.

endo-5-*Bromo*-anti-7-(3-*t*-*butyldimethylsilyloxyoct*-1-*enyl*)*bicyclo*[2.2.1]*heptan*-2-*one* (5).—To a stirred solution of

3-t-butyldimethylsilyloxy-1-iodo-oct-1-ene (1.1 g) in ether (5 ml) at −78 °C under an atmosphere of nitrogen, was added n-butyl-lithium (1.9 ml of a 1.6M solution in hexane). Pentynylcopper (0.43 g) in dry ether (5 ml) and hexamethylphosphorus triamide (0.98 g) was stirred for 30 min, filtered through Hyflo, and added to the solution containing the lithiated side-chain. After 1 h, the tricyclic ketone (4) [4] (0.37 g) in dry dichloromethane (5 ml) was added to the mixture which was then stirred for 3 h at −78 °C. After this a saturated aqueous solution of ammonium chloride (50 ml) was added. The aqueous layer was separated and washed with ether (2 × 50 ml). The combined organic fractions were washed with hydrochloric acid (2M; 3 × 50 ml) and water (2 × 50 ml). The combined aqueous layers were back-extracted with ether (2 × 100 ml). The organic fractions were dried and evaporated to give a yellow oil which was purified by chromatography over silica using ethyl acetate in light petroleum as eluant to give the *bromo-ketone* (5) (0.58 g), $\nu_{max.}$ 1 755 cm^{-1}; δ 5.5 (2 H, m, H-1′ and H-2′), 4.40 (1 H, m, H-5), 4.00 (1 H, m, H-3′), 2.9—1.5 (7 H, m, H-1, 2 × H-3, H-4, 2 × H-6 and H-7) 1.5—1.0 (8 H, m, 4 × CH_2), 1.1—0.65 (12 H, m, 4 × Me), and 0.00 (6 H, s, $SiMe_2$) [Found: (e.i.m.s.) M^+, 428.1743. $C_{21}H_{37}O_2{}^{79}BrSi$ requires M, 428.1735].

anti-8-(3-*t*-*Butyldimethylsilyloxyoct*-1-*enyl*)-2-*oxabicyclo*-[3.2.1]*hept*-6-*en*-3-*one* (8).—*Method* (*a*). To the ketone (5) (1.0 g) in chloroform (25 ml) was added *m*-chloroperoxybenzoic acid (0.46 g) and sodium hydrogencarbonate (0.8 g) with stirring. After 16 h, water (50 ml) and chloroform (40 ml) were added. The aqueous layer was separated and washed with chloroform (40 ml) and the combined organic fractions were washed with water, dried, and evaporated to give the lactones (6) and (13) (95%, ratio 3 : 1 by g.l.c.), $\nu_{max.}$ 1 750 cm^{-1} (Found: M^+, 444.1693. $C_{21}H_{37}{}^{79}BrO_3Si$ requires M, 444.1694). To this mixture of lactones (1.0 g) in toluene (55 ml) was added diazabicycloundecene (DBU) (1.2 g). The mixture was refluxed for 48 h after which it was cooled to room temperature and diluted with water (50 ml); it was then extracted with ether (2 × 50 ml). The combined organic layers were washed with water (2 × 30 ml), dried, and evaporated. The residue was chromatographed over silica using ethyl acetate in light petroleum as eluant to give the *lactone* (8) (62%); $\nu_{max.}$ 1 750 cm^{-1}; δ 6.5 (1 H, m, H-6 or H-7), 6.3 (1 H, m, H-7 or H-6), 5.6—5.3 (2 H, m, H-2′ and H-3′), 4.8 (1 H, m, H-1), 4.0 (1 H, m, H-3′), 3.0—2.6 (4 H, m, H-5, H-7 and 2 × H-4), 1.3 (8 H, m, 4 × CH_2), 0.9 (12 H, m), and 0.1 (6 H, s, $SiMe_2$) [Found: (e.i.m.s.) M^+, 364.2431. $C_{21}H_{36}O_3Si$ requires M, 364.2432].

Method (*b*). To a solution of the ketone (5) (1.0 g) in xylene (25 ml) was added DBU (2.5 g). The mixture was heated under reflux for four days after which it was diluted with water (50 ml) and extracted with ether (2 × 50 ml). The combined organic layers were washed with water (2 × 30 ml), dried, and evaporated. The residue was chromatographed over silica using ethyl acetate in light petroleum as eluant to give the *bicycloheptenone* (7) (0.7 g), $\nu_{max.}$ 1 740 cm^{-1}; δ 6.5 (1 H, m, H-5 or H-6), 6.0 (1 H, m, H-6 or H-5), 5.7—5.5 (2 H, m, H-1′ and H-2′), 4.1 (1 H, m, H-3′), 3.2—1.8 (5 H, m, H-1, H-4, H-7 and 2 × H-3), 1.4 (8 H, m, 4 × CH_2), 0.9 (12 H, m), and 0.1 (6 H, s, $SiMe_2$) {Found: (c.i.m.s.) $[M + NH_4]^+$, 366.2829. $C_{21}H_{36}O_2Si$ requires $[M + NH_4]$, 366.2878}. To a solution of the ketone (7) in chloroform (20 ml) was added *m*-chloroperoxybenzoic acid (2.5 equiv.) and an excess of sodium hydrogencarbonate. After one week, water (40 ml) and chloroform (40 ml) were added. The aqueous layer was separated and washed with chloroform (40 ml) and the combined organic extracts were washed with water, dried, and evaporated to give the *lactone* (8) (72%) as a pale yellow oil.

exo-6-(3-*t*-*Butyldimethylsilyloxyoct*-1-*enyl*)-2-*oxabicyclo*-[3.3.0]*oct*-7-*en*-3-*one* (11).—A solution of the lactone (8) (110 mg) in dry dimethylformamide (DMF) (10 ml) was heated to reflux for 48 h after which it was cooled, diluted with water (20 ml), and extracted with ether (2 × 25 ml). The combined ethereal layers were washed with water (2 × 20 ml), dried, and evaporated. The residue was taken up in dry DMF (5 ml) containing imidazole (51 mg) and t-butyldimethylsilyl chloride (60 mg). After 16 h the mixture was diluted with water (10 ml) and extracted with ether (2 × 20 ml). The combined ether fractions were washed with water (2 × 20 ml), dried, and evaporated. The residue was chromatographed over silica using ethyl acetate in light petroleum as eluant to give the *γ-lactone* (11) identical with an authentic sample [8] (t.l.c. and n.m.r. and i.r. spectroscopy).

5-(3-*t*-*Butyldimethylsilyloxyoct*-1-*enyl*)-4-*hydroxy*-*cyclopent*-2-*enylacetaldehyde* (9).—To a stirred solution of the lactone (8) (0.17 g) in dry, light petroleum (15 ml) at −78 °C was added a solution of di-isobutylaluminium hydride in hexane (20% w/v; 0.38 ml). After 1 h water (10 ml) and sulphuric acid (2 ml) were added. The solution was extracted with ether (2 × 25 ml) and the combined organic extracts were washed with water (2 × 20 ml), dried, and evaporated. The residue was chromatographed over silica using ethyl acetate in light petroleum as eluant to give in the first fractions the *aldehyde* (9) (59%) identical (t.l.c. and n.m.r. and i.r. spectroscopy) with an authentic sample.[6] Evaporation of later fractions gave 5-(3-*t*-*butyldimethyl*-*silyloxyoct*-1-*enyl*)-4-*hydroxycyclopent*-2-*enylethanol* (14) (15%), $\nu_{max.}$ 3 350 cm^{-1}; δ 5.8 (2 H, m, H-2′ and H-3′), 5.6 (2 H, m, H-1″ and H-2″), 4.5 (1 H, m, H-4′), 4.1 (1 H, m, H-3″), 3.7 (2 H, t, 2 × H-1), 2.1—1.6 (6 H, m, 2 × H-2, H-1′, H-5′, and 2 × OH), 1.4 (8 H, m, 4 × CH_2), 0.9 (12 H, s), and 0.1 (6 H, s, $SiMe_2$) [Found: (e.i.m.s.) M^+, 311.2038, $C_{21}H_{38}O_3Si$ requires M, 311.2041].

Reactions of exo-6-(3-*t*-*Butyldimethylsilyloxyoct*-1-*enyl*)-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (11).—(i) *With* m-*chloroperoxybenzoic acid*. To a stirred solution of the lactone (11) (0.36 g) in chloroform (10 ml) was added *m*-chloroperoxybenzoic acid (0.2 g) and sodium hydrogencarbonate (0.1 g). After 48 h the mixture was diluted with water (50 ml) and chloroform (40 ml) and the aqueous layer was separated and extracted with chloroform (40 ml). The combined organic extracts were dried and evaporated. The residue was purified by t.l.c. using ethyl acetate–light petroleum (2 : 3) as eluant to give the epoxide (15) (0.32 g), $\nu_{max.}$ 1 780 cm^{-1}; δ 5.9 (2 H, m, H-7 and H-8), 5.45 (1 H, m, H-1), 3.6—2.2 (7 H, m, 2 × H-4, H-5, H-6, H-1′, H-2′, and H-3′), 1.4 (8 H, m, 4 × CH_2) 0.9 (12 H, m), and 0.1 (6 H, s, $SiMe_2$) {Found (c.i.m.s.) $[M + NH_4]^+$, 398.2785. $C_{21}H_{36}O_4Si$ requires $[M + NH_4]$ 398.2727.

(ii) *With* N-*bromosuccinimide*. A solution of the lactone (11) (0.5 g) and *N*-bromosuccinimide (0.25 g) in dry carbon tetrachloride (25 ml) was irradiated and heated to reflux by a flood-lamp for 45 min. The solution was filtered and the filtrate was washed with water (2 × 25 ml), dried, and evaporated. The residue was chromatographed over silica using ethyl acetate–light petroleum (2 : 3) as eluant to give starting material (0.2 g) and the bromo-ketone (16) (0.1 g), $\nu_{max.}$ 1 780, 1 700, and 1 620 cm^{-1}; δ 6.9 (1 H, dd,

J 16, 7 Hz, H-1′), 6.4 (1 H, d, *J* 16 Hz, H-2′), 6.0 (2 H, s, H-7 and H-8), 5.7 (1 H, m, H-1), 4.4 (1 H, t, *J* 7 Hz, H-4′), 3.8 (1 H, m, H-6), 3.5 (1 H, m, H-5), 2.9—2.4 (2 H, m, 2 × H-4), 2.1—1.9 (2 H, m, 2 × H-5′), 1.5—1.2 (4 H, m, 2 × H-6′ and 2 × H-7′), and 0.9 (3 H, m, Me) {Found (c.i.m.s.) $[M + NH_4]^+$, 346.0846. $C_{15}H_{19}{}^{81}BrO_3$ requires $[M + NH_4]$ 346.0841}.

(iii) *Catalytic hydrogenation*. A solution of the lactone (11) (0.3 g) in dry tetrahydrofuran (25 ml) containing 5% rhodium on alumina (0.2 g) was hydrogenated at room temperature and atmospheric pressure. After 30 min the reaction mixture was filtered through Hyflo. The filtrate was evaporated and the residue was submitted to t.l.c. over silica using ethyl acetate–light petroleum as eluant to give starting material (50 mg) and exo-6-(3-*t*-*butyldimethylsilyloxyoct*-1-*enyl*)-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (17) (0.26 g), $\nu_{max.}$ 1 780 cm^{-1}; δ 5.6 (2 H, m, H-1′ and H-2′), 5.10 (1 H, m, H-1), 4.15 (1 H, m, H-3′), 3.0—1.3 (16 H, m, H-5, H-6 and 7 × CH_2), and 0.9 (12 H, m, 4 × Me), and 0.1 (6 H, s, $SiMe_2$) [Found (e.i.m.s.) M^+, 309.1884. $C_{21}H_{38}O_3Si$ requires *M*, 309.1883].

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